

Exhibit E

ORIGINAL ARTICLE

Induced First-Trimester Abortion and Risk of Mental Disorder

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ABSTRACT

BACKGROUND

Concern has been expressed about potential harm to women's mental health in association with having an induced abortion, but it remains unclear whether induced abortion is associated with an increased risk of subsequent psychiatric problems.

METHODS

We conducted a population-based cohort study that involved linking information from the Danish Civil Registration system to the Danish Psychiatric Central Register and the Danish National Register of Patients. The information consisted of data for girls and women with no record of mental disorders during the 1995–2007 period who had a first-trimester induced abortion or a first childbirth during that period. We estimated the rates of first-time psychiatric contact (an inpatient admission or outpatient visit) for any type of mental disorder within the 12 months after the abortion or childbirth as compared with the 9-month period preceding the event.

RESULTS

The incidence rates of first psychiatric contact per 1000 person-years among girls and women who had a first abortion were 14.6 (95% confidence interval [CI], 13.7 to 15.6) before abortion and 15.2 (95% CI, 14.4 to 16.1) after abortion. The corresponding rates among girls and women who had a first childbirth were 3.9 (95% CI, 3.7 to 4.2) before delivery and 6.7 (95% CI, 6.4 to 7.0) post partum. The relative risk of a psychiatric contact did not differ significantly after abortion as compared with before abortion ($P=0.19$) but did increase after childbirth as compared with before childbirth ($P<0.001$).

CONCLUSIONS

The finding that the incidence rate of psychiatric contact was similar before and after a first-trimester abortion does not support the hypothesis that there is an increased risk of mental disorders after a first-trimester induced abortion. (Funded by the Susan Thompson Buffett Foundation and the Danish Medical Research Council.)

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IT HAS BEEN SUGGESTED THAT AN INDUCED abortion is associated with mental health problems.¹⁻⁴ However, studies addressing this association have had methodologic limitations, including small and self-selected study samples, low response rates and high dropout rates during the follow-up period, lack of control for potential confounders, and inadequate measures of exposure and outcome variables.⁵⁻⁸ In addition, circumstances that make a pregnancy unwanted can themselves be stressful and could be associated with an elevated risk of mental health problems,⁹ resulting in bias. If a woman has an unwanted pregnancy, induced abortion is an alternative to childbirth, which itself is associated with a risk of depression or psychosis.¹⁰⁻¹⁶

Given the public debate regarding a relationship between abortion and mental health problems¹⁷ and the limitations in previous studies, we conducted a cohort study involving national registry data to assess the risk of a first psychiatric contact after first-trimester induced abortion, as compared with before the event; we also looked at the risk of a first psychiatric contact after, as compared with before, childbirth.

METHODS

STUDY POPULATION

Data from the Danish Civil Registration System (CRS), which holds information on all Danish residents, was used to establish an underlying study population of all girls and women born in Denmark between 1962 and 1993 who were alive on their 15th birthday, for a total of 954,702 girls and women.¹⁸ The CRS was established in 1968, when data were recorded for all people alive and residing in Denmark. Among other variables, it includes each resident's personal identification number (CRS number), which is assigned to all Danes at birth or immigration, sex, date of birth, parents' CRS numbers, and daily updated information on vital status. The CRS number is used in all national registers, allowing for an accurate link among data both between and within registers.

MENTAL DISORDERS

Linkage to the Danish Psychiatric Central Register was performed to obtain information on mental disorders in the girls and women in our study population and their parents. There are no private psychiatric hospitals in Denmark, and the

register contains information on all admissions to psychiatric inpatient facilities in Denmark, which has been computerized since 1969.¹⁹ Since 1995, information about outpatient psychiatric contact has also been recorded. At present, the psychiatric register holds information on more than 725,000 persons and 3.25 million contacts. The diagnostic system used was the *International Classification of Diseases, 8th Revision* (ICD-8), from 1969 through 1993,²⁰ with the *10th Revision* (ICD-10) used since 1994.²¹ The girls and women in the study population, as well as their parents, were classified as having a mental disorder if they had records of inpatient or outpatient contact at psychiatric facilities in Denmark for any mental disorder.

INDUCED ABORTIONS

Induced abortions became legal in Denmark in 1973, and any woman (18 years or older) can have a termination of a pregnancy within the first 12 weeks of gestation. Permission from parents or legal guardians is required for pregnant girls under 18 years of age. Approximately 5% of all induced abortions are performed after 12 weeks of gestation; these are permitted primarily for medical or social indications after a request to the regional health and social authorities has been approved.

The Danish National Register of Patients contains data on all admissions to Danish medical hospitals since 1977 and also covers information about all outpatient contact since 1995.²² It includes information on all induced abortions performed in Denmark, except abortions performed by practicing specialists at private clinics in 2005 or later (0.4% of all abortions in 2005, and 2.9% in 2006).²³ From this register, we obtained the dates of first-trimester medical or surgical induced abortions (ICD-10 code O04). Girls and women with records of induced abortions (contact assigned ICD-8 diagnostic code 640, 641, or 642) before January 1, 1995, were excluded from the study to ensure that the sample included only girls and women with a first-ever abortion in the first trimester.

To further ensure that all induced abortions in the study population were first-time abortions, we restricted the population to women and girls born in 1962 or later. This restriction ensured that the oldest members of the cohort were 15 years of age at the time of study entry,

and therefore there was a negligible probability that any member of the cohort had an induced abortion before the start of the register in 1977.

FINAL STUDY POPULATION AND STUDY DESIGN

Our final study population consisted of girls and women born in Denmark between 1962 and 1993 who were alive and had no history of a mental disorder, defined as inpatient psychiatric contact, 9 months before a first-ever first-trimester induced abortion or first childbirth. We excluded girls and women who were born outside Denmark and girls and women emigrating from Denmark (because of the lack of information on psychiatric admissions outside Denmark) and girls and women with records of psychiatric admission occurring before the 9-month period preceding the abortion or childbirth (to ensure that psychiatric contact occurring during the observation period was the first-ever contact for a given patient).

The girls and women in the final study population were followed individually from 9 months before the first-time first-trimester induced abortion or birth of a live infant through 12 months

after the event or until a psychiatric contact occurred for a first mental disorder, until death, until emigration, or until December 31, 2007 — whichever came first. We included only new psychiatric contacts, and we censored follow-up data on the date of the initial contact.

The outcome of interest was the first psychiatric contact (inpatient admission or outpatient visit) for any mental disorder. We compared the 12-month period after the abortion or childbirth with the 9-month period before the event, treating the period before the event as a separate category in analyses. For the main analyses of incidence-rate ratios, the reference category was the period from 9 to 0 months before abortion or childbirth.

There is a potential bias in calculating relative risks on the basis of the period before either abortion or childbirth as the reference group, since the analyses were conditional on the survival of the girls and women during the subsequent 9 months. However, such bias is unlikely, given the relatively young age of the cohort. To address the potential for bias, we performed additional analyses with the period of 11 to 12 months after the abortion or childbirth as the reference group (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

The study was approved by the Danish Data Protection Agency. Written informed consent from the girls and women in the cohort was not required because registry data were used.

STATISTICAL ANALYSIS

Each girl or woman was followed individually by means of survival-analysis techniques. The data were analyzed with the use of a Poisson regression, with the logarithm of the person-years as an offset, and Stata/SE software (version 10.0). This method approximates a Cox regression.^{24,25} We compared the incidence of a first psychiatric contact (per 1000 person-years) between different time periods by calculating incidence-rate ratios, which can be interpreted as relative risks. Age, calendar period, parity status (0 vs. ≥ 1 child at the time of abortion), time since birth or abortion, and presence or absence of a history of mental disorders in parents of the girls and women in the study population were treated as time-dependent variables in prespecified categories.

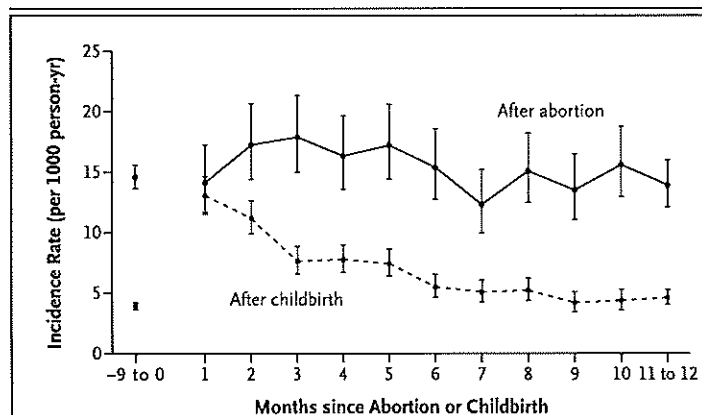


Figure 1. Incidence Rates of First Psychiatric Contact for Any Mental Disorder before and after First-Trimester Induced Abortion or Childbirth.

The incidence rate is the number of new cases divided by the number of person-years at risk. The period -9 to 0 (the reference category) refers to the period from 9 months before the abortion or childbirth to the time of the event. The incidence rates for each of the three trimesters within the 9-month period before childbirth were as follows: first trimester, 3.7 (95% CI, 3.3 to 4.2); second trimester, 4.1 (95% CI, 3.6 to 4.6); and third trimester, 4.0 (95% CI, 3.6 to 4.5). The incidence rates for each of the three 3-month subperiods within the 9-month period before abortion were as follows: months 7, 8, and 9, 14.9 (95% CI, 13.2 to 16.7); months 4, 5, and 6, 14.5 (95% CI, 12.9 to 16.3); and months 1, 2, and 3, 14.5 (95% CI, 12.9 to 16.2). Error bars indicate 95% confidence intervals.

ries.²⁶ Kaplan–Meier estimates of disease-free survival were also plotted for the study population. In addition, we evaluated age, parity status, and presence or absence of a history of mental disorders in the parents as potential effect modifiers by conducting stratified analyses and tests for interaction involving the comparison of the risk of a psychiatric contact in each stratum. Reported P values are two-sided and were calculated with the use of the likelihood-ratio test.

For comparative purposes, we also calculated the incidence rate of a psychiatric contact among girls and women who met the criteria for study entry except that they did not have an abortion or give birth to a child during the study period.

RESULTS

PSYCHIATRIC CONTACT BEFORE AND AFTER ABORTION OR CHILDBIRTH

During the period from 1995 through 2007, a total of 84,620 girls and women had a first-time first-trimester induced abortion. Of these girls and women, 868 (1.0%) had a first psychiatric contact (either inpatient or outpatient psychiatric care) during the 9 months before the abortion, as did 1277 (1.5%) within the 12 months after the abortion. Incidence rates of psychiatric contacts were 14.6 (95% confidence interval [CI], 13.7 to 15.6) per 1000 person-years before abortion and 15.2 (95% CI, 14.4 to 16.1) per 1000 person-years after abortion.

During the same study period, a total of 280,930 girls and women gave birth to their first live-born child. Of these girls and women, 790 (0.3%) had a first-time psychiatric contact within the 9 months preceding delivery, as did 1916 (0.7%) from 0 through 12 months post partum. Incidence rates of psychiatric contacts were 3.9 (95% CI, 3.7 to 4.2) per 1000 person-years before childbirth and 6.7 (95% CI, 6.4 to 7.0) per 1000 person-years after childbirth.

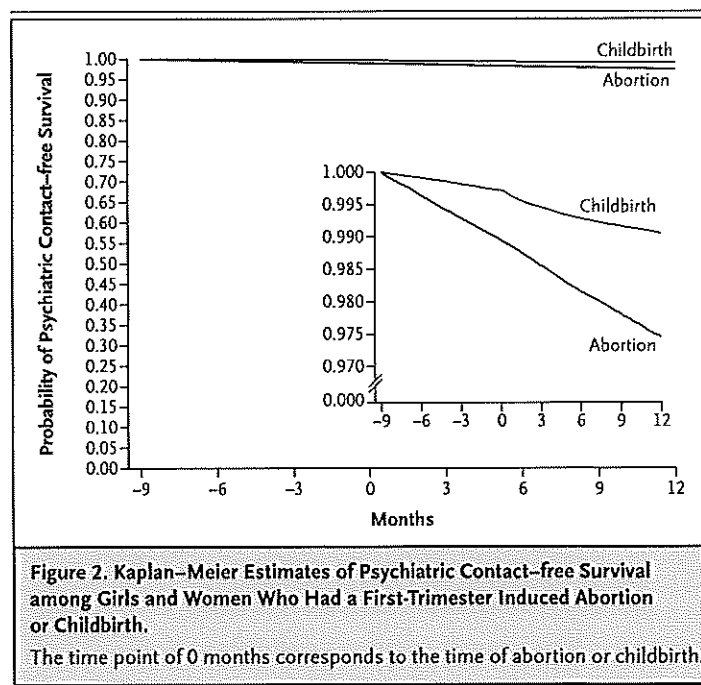
The risk of a psychiatric contact did not differ significantly before and after abortion ($P=0.19$), but the risk after childbirth was significantly greater than the risk before childbirth ($P<0.001$).

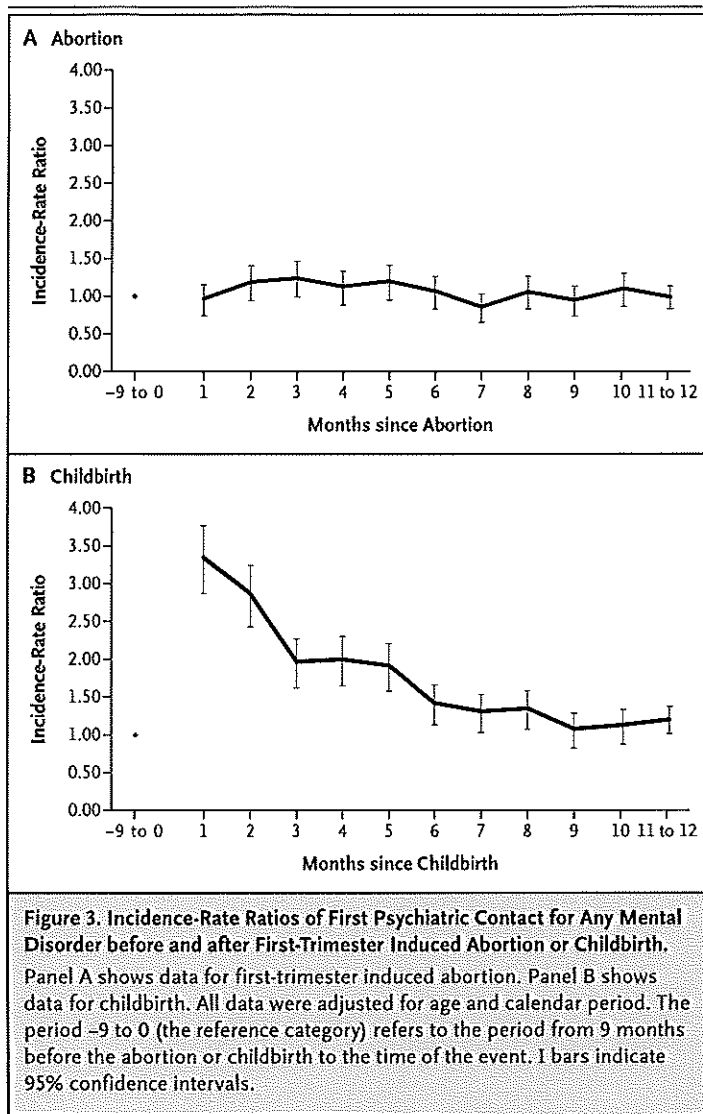
RISK OF PSYCHIATRIC CONTACT WITH ABORTION VERSUS RISK WITH CHILDBIRTH

Figure 1 shows the incidence rates of psychiatric inpatient and outpatient contact before and after

abortion and childbirth. Girls and women who had an abortion had a significantly higher risk of psychiatric contact than girls and women who delivered, except within the first month after the abortion or childbirth. The incidence rate of psychiatric contact among girls and women who did not deliver a child or have an abortion during the entire study period was 8.2 (95% CI, 8.2 to 8.3) per 1000 person-years. In our study population, the incidence rates of psychiatric contact changed around the time of childbirth but not around the time of abortion (Fig. 2).

In 2006, the median ages of the girls and women who had an abortion and those who gave birth were 25.8 years and 28.8 years, respectively. To account for the difference in age distribution and changes during the follow-up period, we calculated incidence-rate ratios with adjustment for age and calendar period (Fig. 3). There was no significant temporal variation in the risk of psychiatric contact before and after first-trimester induced abortions (Fig. 3A). In comparison, the risk of psychiatric contact among girls and women giving birth was increased from the time of birth to 6 months post partum, with the highest observed risk occurring within the first few months after childbirth, as compared with 9 to 0 months before delivery (Fig. 3B).





ADDITIONAL ANALYSES

We performed additional analyses to assess whether the results differed on the basis of the subgroup of mental disorders (Table 1). Psychiatric contact after an abortion was most frequently for neurotic, stress-related, or somatoform disorders. The risk of a first psychiatric contact for these disorders or for personality or behavioral disorders was slightly increased during certain intervals after abortion, as compared with the period before abortion, but there were no consistent increases in risk over time. Similar analyses involving women who gave birth showed a consistent increase in the risk of a new psychiatric contact for neurotic, stress-related, or somato-

form disorders as well as for affective disorders, during the postpartum follow-up period, with the highest observed risks occurring shortly after childbirth (Table 2).

Mental health problems after abortion have been reported to be more frequent in young women than in older women,¹ and a mental disorder in a parent increases the risk of a mental disorder in the offspring,^{27,28} including the risk of a postpartum disorder.²⁹ However, the effect of time relative to abortion on the risk of a psychiatric contact was not significantly affected by age ($P=0.89$ for interaction), parity status ($P=0.09$ for interaction), or the presence or absence of a mental disorder in a parent ($P=0.55$ for interaction).

DISCUSSION

In Denmark, where termination of pregnancy is legal and freely available until the 12th gestational week, we found no significant increase in the incidence rate of psychiatric contact in the 12 months after an induced first-trimester abortion as compared with the 9-month period before the abortion. The incidence rate of psychiatric contact was higher among girls and women who underwent an abortion than among those who underwent delivery, but this relationship was evident before the abortion or childbirth occurred. On the basis of these results, it seems likely that girls and women having induced abortions constitute a population with higher psychiatric morbidity. We interpret this as a selection phenomenon rather than a causal association, since the observed difference in psychiatric morbidity between girls and women having abortions and girls and women delivering antedated the abortion or delivery.

In contrast to our findings, some reports have suggested that abortions might adversely affect mental health. For example, data from a cohort study showed a 30% relative increase in the rate of mental disorders among women having abortions as compared with women not having abortions.³⁰ However, the study was performed in New Zealand, where the majority of abortions are authorized on the basis of mental health indications. This restriction in the availability of abortions can introduce bias,^{31,32} since mental health problems observed after an abortion may reflect conditions and characteristics

Table 1. Diagnosis-Specific Risk of Psychiatric Contact before and after First-Trimester Induced Abortion.*

Interval	Psychiatric Contact for Affective Disorder		Psychiatric Contact for Neurotic, Stress-Related, or Somatoform Disorder		Psychiatric Contact for Personality or Behavioral Disorder		Psychiatric Contact for Any Other Diagnosis	
	no.	relative risk (95% CI)	no.	relative risk (95% CI)	no.	relative risk (95% CI)	no.	relative risk (95% CI)
9–0 Mo before abortion	174	1.00 (reference)	360	1.00 (reference)	90	1.00 (reference)	244	1.00 (reference)
1 Mo after abortion	14	0.69 (0.40–1.18)	50	1.21 (0.90–1.63)	8	0.79 (0.38–1.62)	24	0.89 (0.58–1.35)
2 Mo after abortion	23	1.12 (0.72–1.72)	61	1.47 (1.12–1.93)	10	0.98 (0.51–1.88)	24	0.89 (0.58–1.35)
3 Mo after abortion	20	0.96 (0.60–1.53)	57	1.37 (1.04–1.81)	16	1.56 (0.92–2.66)	30	1.11 (0.76–1.62)
4–6 Mo after abortion	60	0.94 (0.70–1.27)	139	1.10 (0.91–1.34)	45	1.45 (1.01–2.08)	97	1.20 (0.95–1.52)
7–9 Mo after abortion	49	0.75 (0.55–1.03)	129	1.01 (0.83–1.24)	41	1.31 (0.91–1.90)	71	0.88 (0.68–1.15)
10–12 Mo after abortion	51	0.78 (0.57–1.07)	135	1.07 (0.88–1.30)	48	1.55 (1.09–2.21)	75	0.95 (0.73–1.24)

* Data have been adjusted for age and calendar period. Affective disorders were defined as those with an *International Classification of Diseases, 10th Revision* (ICD-10) code of F3X; neurotic, stress-related, or somatoform disorders as those with an ICD-10 code of F4X; and personality or behavioral disorders as those with an ICD-10 code of F6X.

predating the abortion rather than resulting from the abortion.⁷

Another report, from the U.S. National Longitudinal Survey of Youth (NLSY), indicated that women who had abortions were at higher risk for depression than their peers with unplanned pregnancies who delivered.⁴ However, a subsequent reanalysis (involving coding of variables that differed from but were consistent with the original coding scheme and a different strategy for sample selection, which was considered to be less susceptible to bias^{7,8,33}) revealed discrepant results.³³ The NLSY data and the data from the New Zealand study were collected retrospectively and relied on women's willingness to report on potentially sensitive matters such as abortion and mental health.

The New Zealand study³⁰ used interviews to determine diagnoses, classified on the basis of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, and reported, for example, increased risks of anxiety disorders and illicit drug use among women who had an abortion as compared with women with other pregnancy outcomes (including pregnancy loss and childbirth after unwanted or wanted pregnancy). Our study relied on prospectively collected registry information derived from psychiatrists' assessments and diagnoses. We found that psychiatric contact for neurotic, stress-related, or somatoform disorders (ICD-10 codes F40–F48) were the most frequent disorders diagnosed in Danish girls and women within the first year after an

induced abortion (Table 1). Most studies have failed to distinguish between mental health diagnoses such as depression and psychosis and feelings of sadness, loss, or regret, which, although unpleasant, do not necessarily signify a mental disorder.³⁴

In a cohort study of more than 13,000 women with an unwanted pregnancy, the overall rates of psychiatric disorders after abortion were similar to the rates post partum, but differences were observed for diagnosis-specific rates.³⁵ Although childbirth is usually viewed as a happy event, several studies have shown the postpartum period to be associated with an increased risk of both first-time onset and recurrence of a mental disorder.^{10–12,16,36,37}

Women who have an abortion differ in a variety of ways from women who give birth.⁷ We found that the rate of a psychiatric contact differed appreciably between girls and women who had an abortion and girls and women who gave birth, even before the abortion or birth occurred. This suggests that any propensity toward mental health disorders in girls or women who have induced abortions predates the abortion and indeed may make termination of the pregnancy more likely. This finding underscores the potential bias of direct comparisons of rates of mental health problems between girls and women who have undergone abortion and those who have given birth.³¹

The use of population-based registers has both advantages and limitations. The current

Table 2. Diagnosis-Specific Risk of Psychiatric Contact before and after Childbirth.*

Interval	Psychiatric Contact for Affective Disorder		Psychiatric Contact for Neurotic, Stress-Related, or Somatoform Disorder		Psychiatric Contact for Personality or Behavioral Disorder		Psychiatric Contact for Any Other Diagnosis	
	no.	relative risk (95% CI)	no.	relative risk (95% CI)	no.	relative risk (95% CI)	no.	relative risk (95% CI)
9–0 Mo before childbirth	158	1.00 (reference)	355	1.00 (reference)	79	1.00 (reference)	198	1.00 (reference)
1 Mo after childbirth	70	3.79 (2.86–5.02)	146	3.60 (2.97–4.37)	7	0.82 (0.38–1.78)	79	3.56 (2.74–4.62)
2 Mo after childbirth	84	4.51 (3.46–5.87)	127	3.12 (2.54–3.82)	7	0.83 (0.38–1.79)	42	1.89 (1.36–2.64)
3 Mo after childbirth	62	3.30 (2.46–4.42)	84	2.05 (1.62–2.60)	4	0.47 (0.17–1.30)	29	1.30 (0.88–1.93)
4–6 Mo after childbirth	149	2.59 (2.07–3.24)	228	1.84 (1.55–2.17)	20	0.80 (0.49–1.31)	93	1.39 (1.09–1.78)
7–9 Mo after childbirth	100	1.69 (1.31–2.17)	168	1.33 (1.11–1.60)	19	0.77 (0.47–1.28)	63	0.94 (0.70–1.25)
10–12 Mo after childbirth	79	1.29 (0.99–1.70)	149	1.16 (0.96–1.41)	28	1.16 (0.75–1.79)	79	1.17 (0.90–1.52)

* Data have been adjusted for age and calendar period. Affective disorders were defined as those with an *International Classification of Diseases, 10th Revision* (ICD-10) code of F3X; neurotic, stress-related, or somatoform disorders as those with an ICD-10 code of F4X; and personality or behavioral disorders as those with an ICD-10 code of F6X.

study included a large population with low rates of attrition, as well as prospectively recorded information about events and outcomes that did not rely on self-reports. Limitations include the lack of information regarding reasons for terminating the pregnancy and whether the pregnancy was unwanted. It has been suggested that women with unwanted pregnancies who choose to deliver constitute an ideal comparison group in studies on this topic.⁷ Factors contributing to the decision to have an abortion can be distressing^{31,38} and could influence the outcomes of interest. In our study, the outcome of interest was psychiatric contact (inpatient or outpatient); since not all girls and women with mental health problems seek psychiatric care, this measure may underestimate psychiatric morbidity in the cohort. We included only girls and women who did not have a prior psychiatric contact, so we cannot assess whether girls and women with a history of mental disorders had an increased risk of recurrence after abortion or childbirth. Furthermore, the classification of specific psychiatric

diagnoses was based on clinical diagnoses in the registry rather than on research diagnostic criteria. However, previous validation studies have shown close agreement between clinical and research diagnoses.^{39,40}

In conclusion, our study shows that the rates of a first-time psychiatric contact before and after a first-trimester induced abortion are similar. This finding does not support the hypothesis that there is an overall increased risk of mental disorders after first-trimester induced abortion.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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